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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/078,808	02/19/2002	Manas Kumar Majumdar	08702.0086-00000	7146

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EXAMINER	
WOODWARD, CHERIE MICHELLE	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/078,808	MAJUMDAR ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21, 23, 26-28, 32, 35, 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21, 23, 26-28, 32, 35, 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 27 April 2007 has been entered.

Formal Matters

2. Claims 1-20, 22, 24-25, 29-31, and 33-34 have been cancelled by Applicant. New claim 37 has been added. Claims 21, 23, 26-28, 32, 35, and 37 are pending and under examination.

3. Rejections over claims 24-25, 29, 31, 33-34, and 36 are withdrawn as being moot in light of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 112, First Paragraph

New Matter Rejection

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 21, 23, 26-28, 32, 35, and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 21, 26, 27, and 28 recite the phrase "matrix carrier." However, the specification does not recite the term "matrix carrier." Rather, the specification recites "carrier or matrix" (see, i.e., page 16. line 25; paragraph 41). Because the phrase "matrix carrier" does not appear in the specification, nor in the claims as originally filed, the phrase constitutes new matter. An amendment to the claims reciting "matrix," "carrier," or "carrier or matrix" would overcome this rejection. Claims 23, 32, 35, and 37 are rejected as being dependent on rejected claims.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 21, 23, 26-28, 32, 35, and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 21, 26, 27, and 28 recite the phrase "matrix carrier." However, the specification does not recite the term "matrix carrier." Rather, the specification recites "carrier or matrix" (see, i.e., page 16. line 25; paragraph 41). It is unclear whether Applicant is claiming a carrier (as in a carrier for a pharmaceutically administered composition), a matrix (as in a three-dimensional matrix or scaffold), or "a matrix or a carrier." Claims 23, 32, 35, and 37 are rejected as being dependent on rejected claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner

to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. The rejection of claims 21, 23, 26-28, 32, 35, and 37 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,761,887 (Kavalkovich *et al*, PCT Pub WO 00/29552, (the '887 patent) in view of Minas et al., (Orthopedics 1997 Jun; 20(6):525-38), is withdrawn as being moot in light of Applicant's amendments and in light of the new rejection, below.

12. Claims 21, 23, 26-28, 32, 35, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kavalkovich *et al*, (WO 00/29552, 25 May 2000; see also U.S. Patent 6,761,887, 13 July 2004, benefit to 21 June 2001) (previously cited), Minas et al., (Orthopedics 1997 Jun; 20(6):525-38) (previously cited), and Rosen et al., (US Patent 6,034,061, 7 March 2000, benefit to 4 December 1996).

The claims recite a method for inducing chondrogenesis comprising administering to a patient an effective amount of a composition comprising BMP-9, autologous non-tissue culture expanded CD105+ cells isolated from the patient's bone marrow, and a suitable matrix carrier; further comprising BMP-2; a method for treating arthritis comprising administering to a patient an effective amount of a composition comprising BMP-9, autologous non-tissue culture expanded CD105+ cells isolated from the patient's bone marrow, and a suitable matrix carrier; further comprising BMP-2; a method for treating articular cartilage defects or damage comprising administering to a patient an effective amount of a composition comprising BMP-9, autologous non-tissue culture expanded CD105+ cells isolated from the patient's bone marrow, and a suitable matrix carrier; further comprising BMP-2; a method for repairing cartilage tissue comprising administering to a patient an effective amount of a composition comprising BMP-9, autologous non-tissue culture expanded CD105+ cells isolated from the patient's bone marrow, and a suitable matrix carrier; further comprising BMP-2.

Kavalkovich et al., teach a method for inducing chondrogenesis using an alginate layer system formed by seeding mesenchymal stem cells (MSCS) in alginate. These MSCS are known in the art to express CD105 (endoglin) (see, for exemplary purposes only, Barry *et al*., Biochem. Biophys. Res. Comm. 1999, vol. 26541), pp. 134-139; previously cited in the Office Actions of 26 September 2003). Kavalkovich et al., teach that alginate constructs can be formed using non-cultured populations of MSCS (p. 10,lines 10- 19) and that the constructs can be used for cartilage regeneration (p. 5, lines 26-28)and BMP-2 can be included as a chondrogenic agent (p. 8, lines 21-24). Kavalkovich et al., do not

specifically teach a method for inducing chondrogenesis comprising administering autologous non-tissue culture expanded CD105+ cells.

Minas et al., teach the use of autologous cells in allografts and autologous chondrocyte implantation. Minas et al., teach the benefits of autologous cells, including eliminating the known side effects of non-autologous allografts of material that increase the risk of viral transmission, low chondrocyte viability, and the potential for an antigenic immune response against the transplanted cells. The use of autologous cells offers the opportunity to achieve biologic repair without the ensuing complex issues of non-autologous cell rejection or an antigenic or immune response against the non-autologous cells (see pp. 531-535).

Rosen et al., teach methods of using BMP-9 containing compositions in the formation of cartilage (column 2, lines 1-2), the formation of bone (column. 2, line 2), for wound healing and tissue repair (column 2, lines 2-4), and in treating cartilage defects and in the prevention/reversal of osteoarthritis (column 5, lines 37-40). A method of using a composition comprising BMP-9 in conjunction with a composition comprising other BMP proteins, including BMP-2, is taught at column 2, lines 4-12 and 24-34). Example VII (column 19 to column 20) teaches the use of BMP-9 and BMP-2 on articular cartilage proteogylcan and DNA synthesis on explants from calf carpal joints.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Kavalkovich et al., and Rosen et al., with the teachings of Minas et al., to use autologous CD105+ cells with BMP-9 (also known as GDF-2) and BMP-2 as factors that induce chondrogenesis, repair articular cartilage defects, treat arthritis, and repair cartilage tissue because both BMP-9 and BMP-2 have long been known to be involved in chondrogenesis, the formation of cartilage, the formation of bone, and in wound healing and tissue repair (see Rosen et al., *supra*, and Kavalkovitch, et al., *supra*). Additionally, BMP-2 has been shown to interact with endoglin (CD 105) (Kavalkovitch et al., *supra*). Further, the use of autologous cells, as taught by Minas et al., offers the opportunity to achieve biologic repair without the ensuing immunological issues associated with non-autologous cell rejection or the potential for an antigenic or immune response against non-autologous cells. The person of ordinary skill in the art would have been motivated to combine the references because the use of autologous cells is extremely beneficial to the patient without the inherent side effects of non-autologous allografts of material that increase the risk of viral transmission, low chondrocyte viability, and the potential for an antigenic immune response against the transplanted cells. Additionally, Rosen et al., teach the benefits of using BMP-9 alone or in conjunction with other BMPs, including BMP-2, because BMP-9 is significantly effective in stimulating cartilage proteoglycan

synthesis and a combination of cytokines, such as BMP-2 and BMP-9, is more effective in stimulating proteoglycan synthesis than any individual cytokine, alone (Rosen et al., supra, Example VII, column 20, lines 10-15).

In the Remarks, filed 27 April 2007, Applicant argues that the prior cited art (Kavalkovich et al., and Minas et al,) does not provide a reasonable expectation of success in using non-culture expanded cells along with BMP-9 and BMP-2 to induce chondrogenesis. Applicant argues that the use of non-culture expanded cells is more difficult than culture expanded cells because one of skill in the art would not know if the cells will multiply and differentiate in the absence of culture expansion. Applicant argues that the Kavalkovitch et al., reference's recitation of the use of non-tissue culture expanded cells does not actually demonstrate that the use of non-culture expanded cells will actually work to induce chondrogenesis. As such, Applicant's argues that the Kavalkovitch et al., reference does not provide a reasonable expectation of success. Applicant also argues that use of BMP-2 is not a teaching or suggestion to use BMP-9. Applicant's arguments have been fully considered, but are not persuasive.

The evidence of record does not support Applicant's arguments. Kavalkovitch et al., describes numerous uses of non-culture expanded mesenchymal stem cells *in vivo* and *in vitro* in various types of matrices for use in the repair of articular cartilage (pages 1-2). Rosen et al., discuss the modified Sampath-Reddi Assay (Example III, column 10), which demonstrates the effects of new bone and cartilage formation *in vivo*. Additionally the W-20 bioassay (Example VI, columns 17-19) taught by Rosen et al., demonstrates how the *in vitro* activities displayed by the BMP-treated W-20 bone marrow stromal cells correlates with the *in vivo* bone forming activities of BMPs (emphasis added). Minas et al., discuss *in vivo* use of bone marrow stem cells to regenerate articular cartilage as "marrow stimulation techniques" (p. 530, column 1, second paragraph). Minas et al., also cite older studies that were able to trace the origin of the cells proliferating in a rabbit periosteal tibial grafts back to the cells from the graft itself, rather than cells derived from the subcondral bone (p. 530, middle column, first paragraph). Minas et al., also teach methods of *in vivo* studies of knee cartilage replacement surgeries, the results of which have been observed over lengthy periods of time (p. 530, column three, paragraphs 2-4; see also, Table 3, page 535). Minas et al., also teach a method of using mesenchymal cells in a polyglycolic acid polymer (PGA) matrix where the new bone and cartilage formation were tidemarked (p. 541, column 1, paragraph 4; see also paragraph 5, showing *in vitro* results of articular chondrocytes seeded in a collagen matrix correlating with *in vivo* results in a canine model). Using the examples and methods taught by Kavalkovitch et al., Rosen et al., and Minas et al., one of skill in the art would have a reasonable expectation of success in using non-culture expanded cells in the claimed methods.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Friday 9:00am-5:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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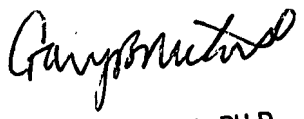

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